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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/767,080	01/22/2001	Madeleine M. Joullie	9596-303U1 (M2163)	5576

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EXAMINER	
MOHAMED, ABDEL A	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 05/06/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/767,080	JOULLIE ET AL.	
	Examiner	Art Unit	
	Abdel A. Mohamed	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 February 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-55* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-55* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3,4*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

ACKNOWLEDGMENT TO IDS, RESTRICTION REQUIREMENT AND STATUS OF THE CLAIMS

1. The information disclosure statement (IDS) and Form PTO-1449 filed 6/28/01 and 7/17/01 and the response to the restriction requirement filed 2/17/04 are acknowledged, entered and considered. Claims 1-55 are present for examination.

ELECTION WITH TRAVERSE

2. Applicant's election with traverse of Group I (claims 1-13, 19-21 and 27-38) in Paper No. 6 is acknowledged. The traversal presented in the election has been considered persuasive for the reasons set forth in the traverse. Hence, the Office action is directed to the merits of claims 1-55 and the previous requirement for restriction has been withdrawn.

OBJECTION TO CLAIMS

3. Applicant is advised that claim 3 is a word for word duplicate of claim 2. Claim 29 is a word for word duplicate of claim 28. Two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

CLAIMS REJECTION-35 U.S.C. § 112 2nd PARAGRAPH

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 1-55 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Independent claims 1, 19 and 27 are indefinite in the recitation "either" because if an ingredient, a step, or other structural element is truly either (i.e., optional), its presence is not necessary for attainment of the result that is an object of the invention, then recitation thereof does not belong in the claims. For clarity, it is suggested to change "either" to –ii) R^2 and R^3 are one of –(See e.g., claim 1 of U.S. Patent No. 6,509,315).

Claims 5, 6, 31 and 32 are indefinite and confusing in referring back to compound 201 (claim 5), compound 203 (claim 6), compound 202 (claim 31) and compound 204 (claim 32) in the specification, respectively because referring back to a Figure or a Table is not acceptable claim language. The designated compound numbers are structures recited as Figures in the instant specification e.g., compounds 201, 202, 203, and 204 are structures, which are shown in Figures 1, 2, 7, and 8 respectively (See e.g., page 5, lines 14-15 in the instant specification). Thus, such material should be incorporated within the claim language. Claims should be complete,

self-contained. Incorporation into claims by express reference to the specification is not permitted and should not be relied on to define the invention (Ex parte Fressola, Bd. Pat. Appl. & Inter., 5/11/93, p. 1608).

Claim 34 is indefinite because the claim does not end with a period. Appropriate correction is required.

Independent claims 44 and 50 are improperly worded Jepson claims (i.e., improvement claims) because Jepson language requires that any independent claim should contain in the following order, (1) a preamble comprising a general description of all the elements or steps of the claimed combination which are conventional or known, (2) a phrase such as "wherein the improvement comprises," and (3) those elements and/or relationship which constitute that portion of the claimed combination which the Applicant considers as the new or improved portion (See 37 CFR 1.75[e]).

CLAIMS REJECTION-35 U.S.C. 112 1st PARAGRAPH.

5. Claims 14-18, 22-26 and 39-43 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for employing compositions comprising any tamandarin or didemnin analogs that have a deoxo-proline residue or a dehydro-proline residue in their structures as recited by the formula recited in claims 1, 19 and 27, and methods of making a tamandarin or didemnin analog by incorporating a deoxo-proline and a dehydro-proline residue in place of a proline residue of the along (claims 44 and 50, respectively), does not reasonably provide methods for inhibiting protein synthesis in a cell by administering the composition of claims 1, 19 and 27 as

recited in claims 14, 22 and 39, respectively, or methods for inhibiting growth of a cell by administering the composition of claims 1, 19 and 27 as recited in claims 15, 23 and 40, respectively, or methods for inhibiting proliferation of a cell by administering the composition of claims 1, 19 and 27 as recited in claims 16, 24 and 41, respectively, or methods for inhibiting tumorigenesis of a cell by administering the composition of claims 1, 19 and 27 as recited in claims 17, 25 and 42, respectively, or methods for enhancing apoptosis of a cell by administering the composition of claims 1, 19 and 27 as recited in claims 18, 26 and 43, respectively. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification does not adequately teach a formulation which is useful for inhibiting protein synthesis, cell growth, cell proliferation, and tumorigenesis, as well as enhancing apoptosis of a cell as recited on page 14, lines 10-18, pages 20-24 and pages 26-38 in instant specification and as presently claimed in claims14-18, 22-26 and 39-43; rather, the specification teaches the employment of compositions comprising tamandarin or didemnin analogs that have a deoxo-proline or a dehydro-proline residues in their structures as represented in formula I and to a method of making such compositions thereof by incorporating deoxo-proline and dehydro-proline residues in place of a proline residue of the analogs, respectively as disclosed on pages10-20, Examples 1 and 2, and Figures 3-6. Figures 3-5 and Example 1 show a method of making deoxo-proline-containing side chain moieties for tamandarin or didemnin analogs. Figure 6 and Example 2 demonstrate a method of making dehydro-proline-

containing side chain moieties for tamandarin or didemnin analogs. However, no factual evidence or data or example(s) are presented except protocols to show that tamandarin or didemnin analogs claimed to be administered *in vitro* to a cell or tissue (e.g., a cultured cell or tissue, or a cell or tissue harvested from one animal prior to introduction into the same or different animal). Alternatively, the analogs can be administered to the cell or tissue *in vivo* by administering the analog or a pharmaceutical composition comprising the analog to an animal (e.g., a mammal such as a human) that comprises the cell or tissue as stated on page 23, lines 12-17 in the instant specification and in the manner claimed in claims 14-18, 22-26 and 39-43.

Therefore, the instant specification does not commensurate with the claimed subject matter in which the compositions comprising deoxo-proline or dehydro-proline tamandarin and didemnin analogs are administered for inhibiting protein synthesis, cell growth, cell proliferation, and tumorigenesis, as well as enhancing apoptosis of a cell as disclosed above and claimed in claims 14-18, 22-26 and 39-43. There is no evidence in the instant specification to use or administer the various compositions in the manner claimed. The scope of the instantly claimed invention are very broad and speculative in that the various deoxo-proline–containing and dehydro-proline-containing tamandarin and didemnin and their analogs as claimed can represent virtually any family of tamandarin and didemnin, and as such, the scope of the claims are extremely broad and relate to a very large number of possible tamandarins and didemnins of which some of them are cytotoxic.

For support, see the reference of Grubb et al. (Bichem. Biophys. Res. Commun., Vol. 215, No. 3, pp. 1130-1136, 1995) which states on page 1130 that the mechanism by which didemnin B induces its cytotoxic effect on cells remains obscure. Although, didemnin has been shown to posses potent neoplastic and anti-viral activity *in vitro* and *in vivo*, however, it is considered to be the most cytotoxic member of the didemnin family. Similarly, the reference of Pfizenmayer et al. (Bioorg. Med. Chem. Lett., Vol. 8, pp. 3653-3656, 1998) on page 3653 states that didemnin B which is one of the most potent natural members of the didemnin family, has shown antiviral, antitumor, and immunosuppressant activities is found to display some side effects such as hepatic toxicity and neuromuscular toxicity. Also, didemnin B was shown to be very cytotoxic to lymphocytes. Further, Applicant acknowledges on page 2, lines 14-20 in the instant specification by stating that despite the potency of didemnin B in isolated studies, its clinical effectiveness is hampered by the side effects associated with therapeutic doses of the compound. As with many anti-proliferative agents, didemnin B exhibits a relatively narrow therapeutic window. Although, didemnin M and dehydrodideminin B exhibit improved therapeutic potential, relative to didemnin B, a need still exists for anti-proliferative agents, which exhibit less toxicity at a therapeutic dose (i.e., didemnin analogs having a greater therapeutic index).

Thus, in view of the above, and in view of their potential cytotxicity, there are no sufficient data or evidence or working example(s), which show that the claimed compositions of tamandarin and didemnin and their analogs are useful in the methods of, claims 14-18, 22-26 and 39-43 in the manner claimed. Hence, the only support of

the claimed pharmaceutical formulation and their methods of use in the specification is Applicant's supposition of the invention as recited in the protocols. Thus, one of ordinary skill in the art cannot administer any or all tamandarin or didemnin family members including their analogs which are considered to be cytotoxic as discussed above and supported by Applicant's acknowledgment and by the references of Grubb et al. or Pfizenmayer et al. in all situations claimed without appropriate testing.

Therefore, the claims are based on pure speculation that the methods would be effective since Applicant has not established any *nexus* between the claimed compositions and their use in the manner claimed. Thus, in view of the above, it would include those that have not been shown or taught to be useful or enabled by the disclosed method of making and using the invention. Further, undue experimentation is necessary to determine if and under what conditions, the claimed invention as broadly claimed is enabled, since a vast range of composition in a variety of analogs are contemplated and are encompassed as well as wide range of situations (i.e., various kinds of inhibitions such as protein synthesis, growth of a cell, proliferation of a cell, and tumorigenesis in a cell). The results desired appear to be highly dependent on all variables, the relationship of which is not clearly disclosed. Hence, one of ordinary skill in the art would not be able to identify all the compositions/formulations with wide range of administering (i.e., *in* vitro or *in* vivo) intended to effective for the claimed purpose of inhibition or enhancement of the various methods as encompassed in the claims would be effective and under what conditions.

Further, the first paragraph of 35 U.S.C. 112 requires, *inter alia*, that a patent specification provide sufficient guidance to enable a person skilled in the art to make and use the claimed invention without undue experimentation. *In re Vaeck*, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991). While patent Applicants are not directed to disclose every species that falls within a generic claim, id. At 496, 20 USPQ2d at 1445, it is well settled that "the scope of the claims must bear a reasonable correlation to the scope of the enablement provided by the specification". *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Where practice of the full scope of the claims would require experimentation; factors to be considered in determining whether a disclosure would require undue experimentation ..... include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. *In re Wands*, 858 F. 2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

Therefore, in view of the above, and in view of the fact that there is no enablement in the instant specification for methods of inhibiting protein synthesis, cell growth, cell proliferation, and tumorigenesis, as well as enhancing apoptosis of a cell by administering the various compositions in the manner claimed in claims 14-18, 22-26 and 39-43. Thus, applying the *Wands* factors to the facts of this case, one of skill in the art would find that undue amount of experimentation would be required to practice the full scope of the extremely broad claims for the reasons given above. Hence, in view of

the quantity of experimentation necessary, the lack of adequate guidance or working example(s) or data or evidence, and the breadth of the claims, the claims are not commensurate in scope with the enabling disclosure. Accordingly, filing of evidence commensurate with the scope of the claims or amendment of the claims to what is supported by the enabling disclosure is suggested.

CITATION OF RELEVANT PRIOR ART

6. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure:

Liang et al. (J. Am. Chem. Soc., Vol. 123, pp. 4469-4474, 2001) discloses total synthesis and biological investigations of tamandarins A and B and tamandarin A analogs.

CONCLUSION AND FUTURE CORRESPONDENCE

7. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Abdel A. Mohamed number is (571) 272-0955. The examiner can normally be reached on Monday through Friday from 7:30 a.m. to 5:00 p.m. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can be reached on (571) 272-0951. The appropriate fax phone number for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 305-7401 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

CHRISTOPHER S. F. LOW
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Mohamed/AAM

April 30, 2004